

washed with 10 ml of diethyl ether. To the filter cake, 10 ml of 10% acetic acid aqueous solution (hereinafter referred to as aqueous acetic acid) was added and the mixture was stirred for 30 minutes. The resin was then filtered, and washed with 4 ml of aqueous acetic acid. After lyophilizing the filtrate and the wash, the crude peptide obtained was dissolved in aqueous acetic acid, and injected into a reverse phase packing material COSMOSIL 5C18-AR column (25  $\phi$  x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased up to 25% over 260 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 11.7 mg of Lys-Phe-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO:1).

Please replace the paragraph beginning on page 46, line 11 with the following amended paragraph:

The peptide obtained, Lys-Phe-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO:1), had a retention time of 23.9 minutes in an analysis using a reverse phase packing material YMC-PACK ODS-AM column (4.6  $\phi$  x 250 mm) eluted with a linear gradient of acetonitrile concentration from 0 to 60% containing 0.1% TFA, and the results of amino acid analysis and mass spectrometry of the product were consistent with the theoretical values.

Please replace the paragraph beginning on page 47, line 22 with the following amended paragraph:

Synthesis of Asp-Phe-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO: 2)

In the same manner as that described in Example 5, using 100 mg of Fmoc-Phe-Alko Resin, Fmoc-Asp (OtBu)-OH, Fmoc-Gly-OH, Fmoc-Gly-OH, Fmoc-Gln-OH, Fmoc-Ile-OH, Fmoc-Met-OH, Fmoc-Phe-OH, and Fmoc-Asp(OtBu)-OH were coupled in order, and the product was then deprotected. The crude peptide obtained was dissolved in aqueous acetic acid and injected into a reverse phase packing material COSMOSIL 5C18-AR column (25  $\phi$  x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased up to 31% over 260 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 3.6 mg of Asp-Phe-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:2).

Please replace the paragraph beginning on page 48, line 10 with the following amended paragraph:

--The peptide obtained, Asp-Phe-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:2), had a retention time of 25.8 minutes in an analysis using a reverse phase packing material YMC-PACK ODS-AM column (4.6  $\phi$  x 250 mm) eluted with a linear gradient of acetonitrile concentration from 0 to 60% containing 0.1% TFA,

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and the results of amino acid analysis (Met being not detected) and mass spectrometry of the product were consistent with the theoretical values.

Please replace the paragraph beginning on page 50, line 2 with the following amended paragraph:

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-- The peptide Lys-Tyr-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO: 39) was synthesized in the same manner as that described in Example 5. Specifically, using 100 mg of Fmoc-Phe Alko Resin, Fmoc-Asp (OtBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Val-OH, Fmoc-Arg(Pmc)-OH, Fmoc-His(Trt)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Lys(Boc)-OH were coupled in order, and the product was then deprotected. The crude peptide obtained was dissolved in aqueous acetic acid and injected into a reverse phase packing material COSMOSIL 5C18-AR column (25  $\phi$  x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased up to 25% over 200 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 44.9 mg of Lys-Try-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO:39).

Please replace the paragraph beginning on page 50, line 17 with the following amended paragraph:

*Bj*  
-- The peptide obtained Lys-Tyr-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO:39) had a retention time of 17.7 minutes in an analysis using a reverse phase

packing material YMC-PACK ODS-AM column (4.6  $\phi$  x 250 mm) eluted with a linear gradient of acetonitrile concentration from 0 to 60% containing 0.1% TFA, and the results of amino acid analysis and mass spectrometry of the product were consistent with the theoretical values.

Please replace the paragraph beginning on page 51, line 15 with the following amended paragraph:

Synthesis of Asp-Tyr-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO: 40)

In the same manner as that described in Example 5, using 100 mg of Fmoc-Phe-Alco Resin, Fmoc-Asp (OtBu)-OH, Fmoc-Gly-OH, Fmoc-Gly-OH, Fmoc-Gln-OH, Fmoc-Ile-OH, Fmoc-Met-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Asp(OtBu)-OH were coupled in order, and the product was then deprotected. The crude peptide obtained was dissolved in aqueous acetic acid and injected into a reverse phase packing material COSMOSIL 5C18-AR column (25  $\phi$  x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased up to 27% over 200 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 12.8 mg of Asp-Tyr-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:40).

Please replace the paragraph beginning on page 52, line 3 with the following amended paragraph:

--The peptide obtained Asp-Tyr-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:40) had a retention time of 24.7 minutes in an analysis using a reverse phase packing material YMC-PACK ODS-AM column (4.6  $\phi$  x 250 mm) eluted with a linear gradient of acetonitrile concentration from 0 to 60% containing 0.1% TFA, and the results of amino acid analysis (Met being not detected) and mass spectrometry of the product were consistent with the theoretical values.

Please replace the paragraph beginning on page 56, line 7 with the following amended paragraph:

--To this peptide resin, 1 ml of Reagent K (5% phenol, 5% thioanisole, 5% H<sub>2</sub>O, and 2.5% ethanedithiol in TFA) was added and allowed to react for 2.5 hours at room temperature. While cooling with ice, 10 ml of diethyl ether was added to the reaction, the mixture was stirred for 10 minutes, filtered, and then washed with 10 ml of diethyl ether. To the filter cake, 10 ml of aqueous acetic acid was added and the mixture was stirred for 30 minutes. The resin was then filtered, and washed with 4 ml of aqueous acetic acid. After lyophilizing the filtrate and the wash, the crude peptide obtained was dissolved in aqueous acetic acid, and injected into a reverse phase packing material YMC-PACK ODS-A SH-363-5 (30  $\phi$  x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased from 0 to 15% over 60 minutes and from 15% to 30% over 240 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored

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*by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 9.7 mg of Gly-Phe-Met-Cys-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:41).--*

Please replace the paragraph beginning on page 56, line 25 with the following amended paragraph:

--The peptide obtained, Gly-Phe-Met-Cys-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:41), was analyzed using a reverse phase packing material YMC-PACK ODS-AM AM303 (4.6 φ x 250 mm), and proved to have a retention time of 18.8 minutes with a linear gradient of acetonitrile concentration from 18% to 48% containing 0.1% TFA. The results of amino acid analysis (Cys could not be detected) and mass spectrometry of the product were consistent with the theoretical values.--

*γ12 Please replace the Sequence Listing filed December 22, 2000 located immediately after the abstract with the substitute Sequence Listing enclosed herewith.*

#### REMARKS

Enclosed herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a substitute Sequence Listing to be inserted into the specification as indicated above. The substitute Sequence Listing in no way introduces new matter into the specification.

Also submitted herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a disk copy of the substitute Sequence Listing. The disk copy of the substitute Sequence Listing, file "0020-4792P.ST25", is identical to the paper copy, except that it lacks formatting.